Record Review

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THE CHEMICAL RECORD

Recent Advances in the Electrochemical Synthesis of Organosulfur Compounds

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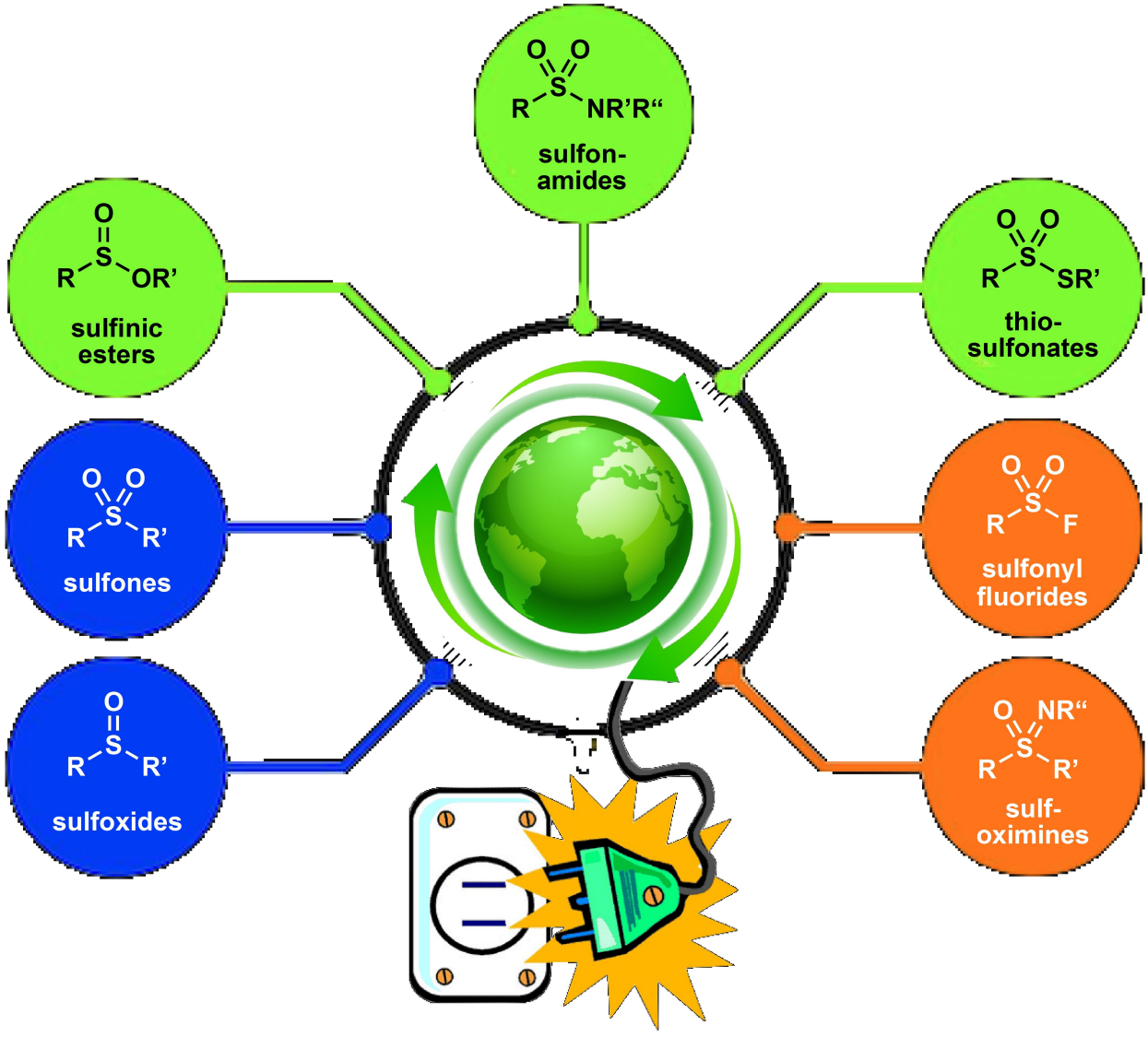

Abstract: Organosulfur compounds are being widely used in medicinal chemistry, as well as in organic transformations and in synthetic applications. Because of their interest in many areas, the development of sustainable and green synthetic methods to access various organosulfur compounds has a high influence on the chemistry community. Electroorganic synthesis has become a very valuable methodology for the synthesis of organosulfur compounds during the last decade. The use of electrochemical technology offers a green, sustainable and safe alternative to prepare and modify such compounds. This review summarises recent developments in the preparation of organosulfur compounds such as sulfoxides, sulfones, sulfinic esters, sulfonamides, thiosulfonates, sulfonyl fluorides and sulfoximines under electrochemical reaction conditions.

Keywords: batch electrolysis, electrochemistry, flow reactors, organosulfur compounds, oxidation

1. Introduction

Organosulfur compounds are occurring in abundance in natural products, bioactive compounds and materials as main functional units.[1] Sulfur can exist in several oxidation states in nature at −2, 0, +2, +4 and +6. Most abundant in the earth's crust is the dianion of sulfuric acid (H_2SO_4) in which sulfur has an oxidation state of +6. Sulfur monoxide has sulfur in +2 oxidation state while sulfur dioxide has sulfur in the +4 oxidation state. Also, the S–S bond exists in three of the more common forms of inorganic oxygenated sulfur ions, dithionates, trithionates and thiosulfates.[2] They also are important in medicinal and pharmaceutical compounds as well as in organic transformations and applications (Figure 1).[3,4] The oxygen of the sulfinyl group has the ability to coordinate with ligands, metal ions, or electron pairs. The stereoelectronic effects and the conformational stability that exists in the sulfinyl group, in sulfoximines and chiral sulfoxides provide stable molecules which have been used as ligands in asymmetric catalysis and as chiral auxiliaries in stereoselective synthesis.[5,6] Taking into account the value of organosulfur oxidation processes, many efforts have been made to develop more sustainable oxidative methods that have a major impact on the industry in reducing chemical waste, toxic by-products and costs. Generally, the oxidation of organosulfur compounds can be achieved with peroxides,[7,8] hypervalent iodine reagents[9,10] or through photocatalytic processes.[11] Despite the various documented procedures, the oxidation processes for organosulfur compounds are often constrained by a difficult scale-up, by low sustainability and the use of hazardous oxidising reagents.

The development of simple, intrinsically green and safe methods for the formation of S–X bonds has attracted interest of organic chemists. Electrochemical technology has emerged as a green, sustainable and safe alternative to prepare such compounds.[12,13] In electrochemical synthesis, electrons are being used as green oxidant and as an alternative to chemical oxidants. Recently, the use of anodic oxidation along with cathodic reduction has been extensively employed in organic synthesis. An oxidation-reduction (redox-) reaction occurs by gaining electrons at the anode (oxidation) and losing electrons at the cathode (reduction). The direct oxidation/reduction where the electron exchange happens at the electrode surface, is a heterogeneous process. Sometimes such heterogeneous electron transfers require large overpotential at the electrodes. To overcome this, a mediator can be used which can

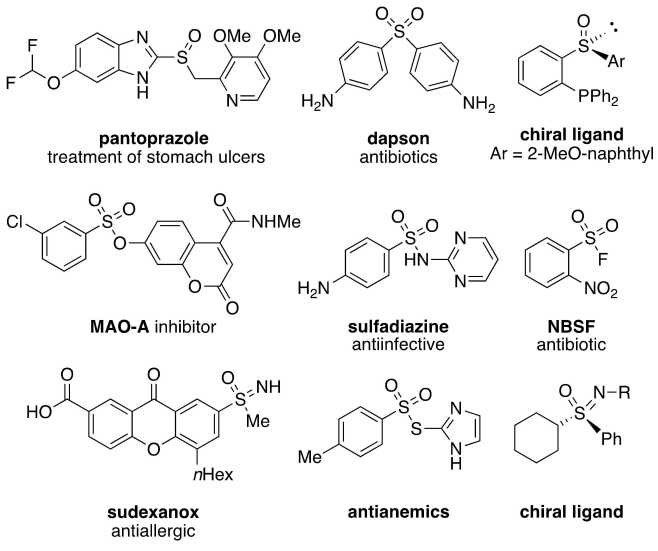

Figure 1. Examples of sulfur-containing natural products, pharmaceuticals and chiral ligands.

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participate in the heterogeneous electron transfer process with the electrode. The electrons can be shuttled to the organic molecule in a homogenous process. The electrode where the desired reaction takes place is termed as "working" electrode, while the other electrode is attributed as the "counter" or "auxiliary" electrode. Depending on the type of transformation, either an undivided or a divided cell can be used. In an undivided cell, both electrodes are placed in the same solution while in a divided cell, two different cell compartments containing an electrode each are connected by a salt bridge or a membrane suitable for ion transport. The same arrangement is possible in flow reactors.[14,15] Compared to traditional strategies, electrochemical methods are reliable, sustainable and have a high atom economy in chemical synthesis.

This review presents recent electrochemical developments of organosulfur chemistry that have been published within the last 10 years. Although this review primarily includes references after 2000, some previous papers are also mentioned to provide a context to the topic. Electrochemical applications in the synthesis of sulfur derivatives shown in Figure 2 are summarised.

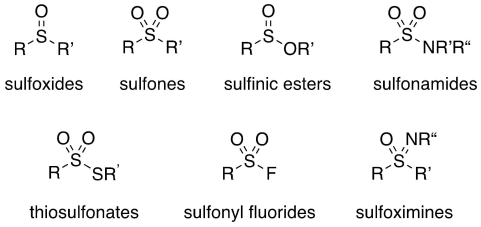

Figure 2. Overview of organosulfur compounds.

2. Electrochemical Synthesis of Sulfoxides and Sulfones

In a large range of functional organic molecules, sulfoxide and sulfone moieties are common. Several pharmaceutical compounds[16–18] such as Dapsone, Esomeprazole, Ponazuril, Pantoprazole, Ajoene and Sulmazole and even polymeric materials[19] contain such moieties. In addition, chiral sulfoxides have been used as ligands and as chiral auxiliaries in asymmetric transition-metal catalysed transformations.[20]

In 2017, Noël and co-workers[21] have described the direct oxidation of thioethers **1** selectively to corresponding sulfoxides **2** or sulfones **3** by potentiostatic electrolysis under flow reaction conditions. Although supporting electrolytes have to be added, the selectivity was controlled by the applied potential and the residence time. This protocol was successful to transform a broad range of thioethers into their sulfoxides or sulfones in moderate to excellent yields (Scheme 1) while tolerating several functional groups including different nitrogen-containing heteroaromatic compounds without *N*-oxide formation.

Subsequently, in 2018 Huang and co-workers[22] described the electrochemical synthesis of sulfoxides **6** from thiophenols/aliphatic thiols **4** and dimethyl sulfoxide (DMSO) **5**. This protocol performed the oxidation by using hydrogen peroxide and electrons as oxidants. The reaction proceeded under galvanostatic reaction conditions with platinum electrodes and the addition of 20 mol% $FeCl_2$ catalyst and a supporting

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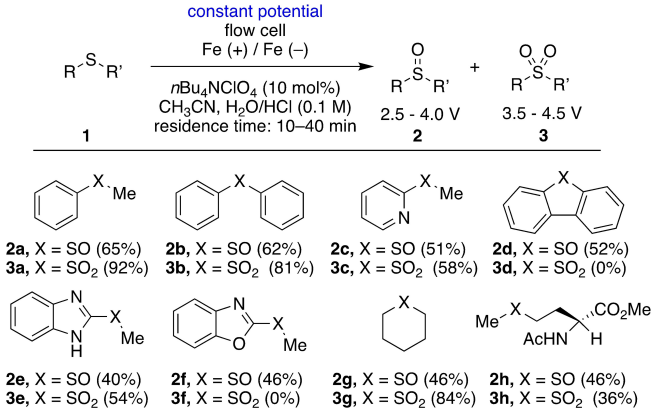
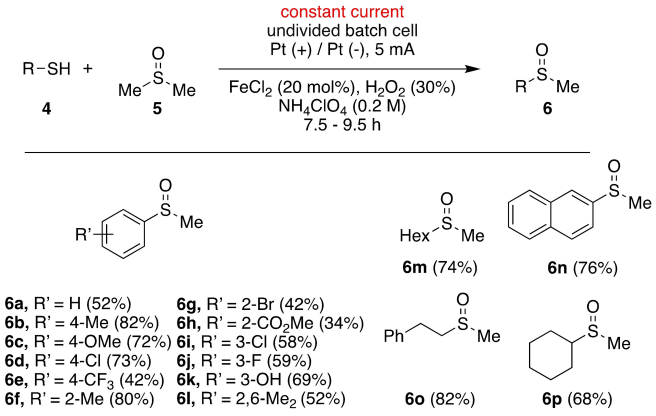
Thomas Wirth is professor of organic chemistry at Cardiff University. After receiving his PhD from TU Berlin, he went to Kyoto University as a JSPS fellow. Then he worked independently at the University of Basel before taking up his current position at Cardiff University in 2000. He was awarded the Werner Prize by the New Swiss Chemical Society, the Wolfson Research Merit Award by the Royal Society, and the Bader Award by the Royal Society of Chemistry. In 2016 he was elected as a fellow of The Learned Society of Wales. His main research interests concern stereoselective electrophilic reactions oxidative transformations with hypervalent iodine reagents, and flow chemistry including electrochemistry performed in microreactors.

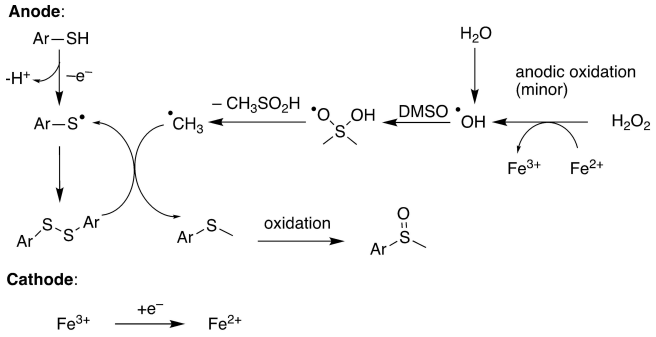


Scheme 1. Electrochemical oxidation of thioethers to sulfoxides and sulfones in flow electrochemistry using potentiostatic reaction conditions.

electrolyte. It is proposed that a sulfur radical generated from thiol **4** reacts with a methyl radical generated upon addition of a hydroxyl radical to DMSO **5**. The thioether is subsequently oxidised to the sulfoxide (Scheme 3). A wide range of different



Scheme 2. Electrochemical galvanostatic synthesis of sulfoxides from thiols and dimethyl sulfoxide in an undivided batch cell.

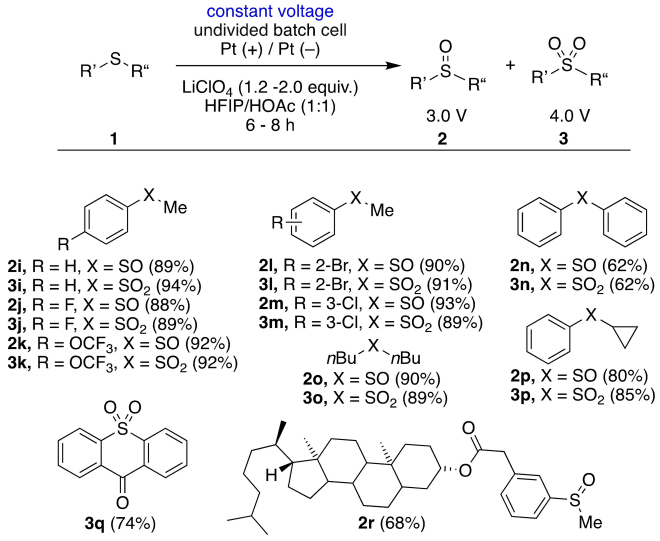


Scheme 3. Proposed mechanism for the electrochemical synthesis of sulfoxides from thiols and DMSO (dimethyl sulfoxide).

substituted thiophenols were converted to the corresponding sulfoxides in moderate to good yields (Scheme 2).

In 2019, Xu and co-workers[23] reported an efficient and selective electrochemical oxidation of thioethers **1** to sulfoxides **2** and sulfones **3**. The authors proposed that the hydrogen bonding between hexafluoro-2-propanol (HFIP) and acetic acid (AcOH) used as the solvent mixture plays a significant role in the oxidation protocol. Strong hydrogen bonding with the sulfoxide prohibited further oxidation at oxidation potentials around 3.0 V. Therefore, a selective oxidation of thioethers to sulfoxides was achieved without any over-oxidation. This investigation was supported by the DFT calculations and cyclic voltammetry experiments. The optimum conditions were obtained with platinum anode and cathode electrodes, with stoichiometric amounts of $LiClO_4$ as electrolyte. Access to sulfones was achieved at oxidation potentials >4.0 V. A broad range of thiophenols with different substituents resulted the corresponding sulfoxides and sulfones in moderate to good yields (Scheme 4). Interestingly, this procedure also tolerated sulfide containing natural product skeletons (**2r**).

Very recently (2021), Jiao and co-workers[24] established an alternative electrochemical approach by using a simple and readily available Ni(II) salt as the electrocatalyst and water as the oxygen source for the selective oxidation of sulfides **1**. This protocol showed the efficiency of nickel catalysis for oxygen-atom transfer reaction under mild electrochemical conditions in one step. The use of electricity to reduce the stable Ni(II) complex for O_2 activation, along with a further one-electron reduction of the produced Ni(II) superoxo intermediate to the active Ni(II) peroxo species, illustrates the possibilities



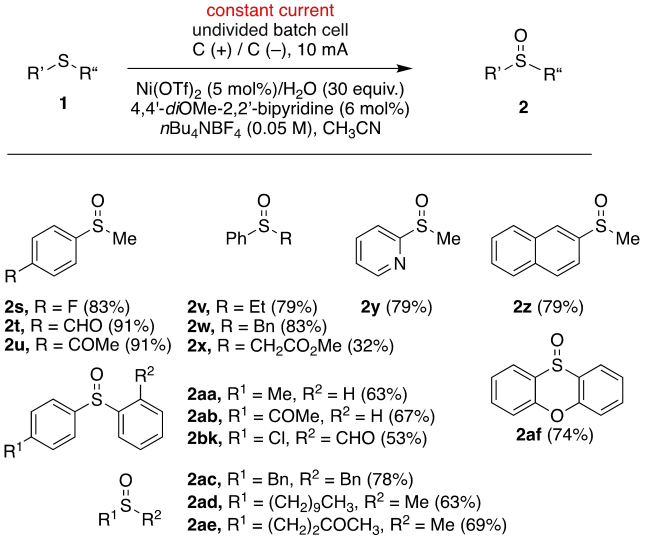
Scheme 4. Electrochemical oxidation of thioethers to sulfoxides and sulfones in batch electrochemistry using potentiostatic reaction conditions.

associated with electrochemical activation methods. The reaction was conducted in an undivided cell with graphite electrodes under galvanostatic reaction conditions and catalytic amounts of $Ni(OTf)_2$ with nBu_4NBF_4 as a supporting electrolyte using water (30 equiv.) as the oxygen source. The use of 4,4′-dimethoxy-2,2′-bipyridine as ligand gave highest yields (Scheme 5). However, the yield dropped significantly in absence of the Ni(II) catalyst.

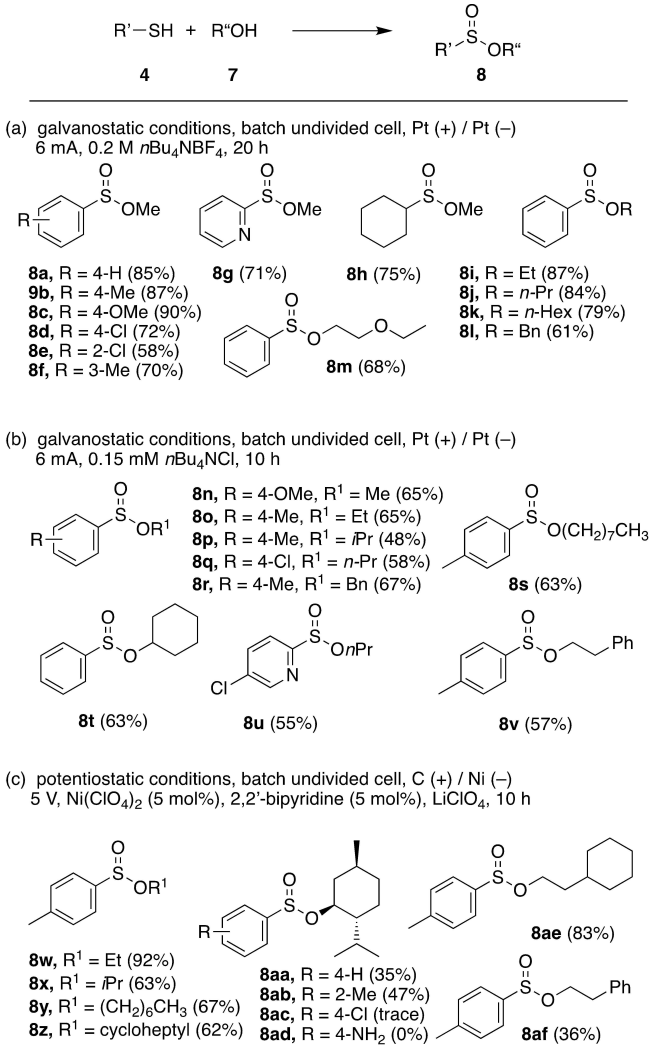
3. Electrochemical Synthesis of Sulfinate Esters

Sulfinate esters are promising structures in medicinal chemistry, they are also found in biochemical applications[25] and as intermediates in synthesis.[26,27] A variety of sulfinate esters is commercially available having medicinal and biological applications. Moreover, sulfinate esters play an essential role in chiral sulfur reagents[28,29] and have been used as important intermediates in synthesis.[30]

Several reports on electrochemical methods for the synthesis of sulfinic esters **8** in a direct reaction between thiols **4** and alcohols **7** have been reported recently. The first example of an electrochemical S–O coupling was developed by Zhong and co-workers in 2019.[31] The reaction tolerates various functional groups and also can be performed on a large scale, affording sulfinate esters in moderate to excellent yields under mild reaction conditions (Scheme 6a). Different thiols and alcohols were used under standard conditions in an undivided batch electrochemical cell with platinum electrodes and *n*-Bu_4NBF_4 as electrolyte. Almost similar reaction conditions were reported by Wei (Scheme 6b).[32] The over-oxidation to



Scheme 5. Electrocatalytic oxidation of thioethers to sulfoxides in batch electrochemistry using potentiostatic reaction conditions.



Scheme 6. Electrochemical oxidation of thiols to sulfinic esters.

sulfonate esters was successfully prohibited by controlling the current. Kaboudin and co-workers[33] synthesized the sulfinate esters in a nickel-catalysed oxidative esterification of thiols **4** with alcohols **7** (Scheme 6c). The reaction starts with an anodic oxidation of thiyloxy-Ni(I) to a sulfinate-Ni(III) and a cathodic reduction of the nickel complex to Ni(0). Thus, the sulfinate esters **8** were obtained in reasonable yields through the potentiostatic electrolysis.

4. Electrochemical Synthesis of Sufonamides

Although uncommon in natural products,[34] several biological and medicinal processes involves sulfonamides.[35–37] These compounds are also used for the preparation of various

carbonyl compounds, aromatic carbo- and heterocycles, and also as organocatalysts in asymmetric synthesis.

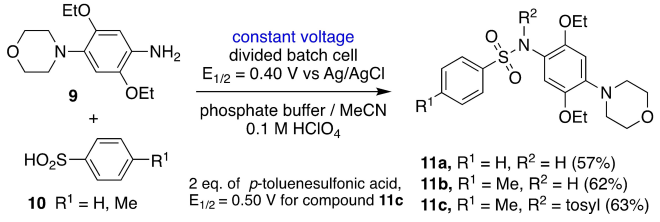
In 2014, Beiginejad and Nematollahi[38] synthesised sulfonamides **11** by using an electrochemical process (Scheme 7). The reaction is performed in a divided cell under constant voltage through the reaction between aniline **9** and sulfinic acids **10** in the presence of $HClO_4$ (0.1 M) to form sulfonamides **11**.

An efficient electrochemical synthesis of sulfonamides **14** through the reaction between amines **12** and sodium sulfonates **13** in the presence of 50 mol% of NH_4I as mediator and supporting electrolyte was disclosed in 2016 by Zeng and co-workers (Scheme 8).[39] In this process, sulfinates were used as the sulfonyl sources via a single electron transfer leading to the sulfonamide products in good yields. The sulfonamides were obtained using carbon as anode and nickel as cathode electrode material using an undivided cell. The broad reaction scope (22 examples) was complemented with the use of ammonia as a suitable amine to produce 4-methylbenzenesulfonamide **14a** in 61% yield. At the same time, Yuan[40] and Terent'ev[41] also developed the electrochemical oxidative cross coupling reaction between amines and sodium sulfinates in the presence of iodide salt as catalyst.

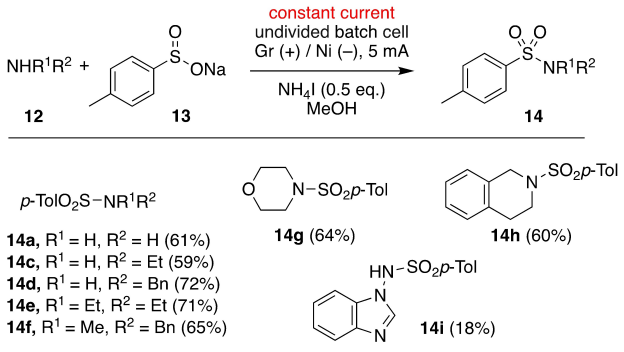
The electrochemical synthesis of sulfonamides was transferred and further optimised in flow systems by the Noël group.[42] The flow protocol led to the targeted sulfonamides **15** in only 5 minutes without using any additional reagents or catalysts. By direct anodic coupling of amines **12** and thiols **4**, a wide array of substrates were examined offering products in moderate to good yields (Scheme 9).

Subsequently, Nematollahi and co-workers reported another electrochemical route for the synthesis of sulfonamides in aqueous solutions.[43,44] The same technique was used for the electrochemical synthesis of new halo-*N*-hydroxysulfonamide derivatives.[45] These compounds were synthesised in an undivided electrochemical cell. The proposed mechanism of this development showed that the halonitroarene is reduced at the cathode to generate hydroxylamines which are then transformed to the halonium acceptor intermediate by oxidation at the anode (Scheme 11). Using different nitrobenzenes and benzenesulfinic acids a total 11 examples were reported (Scheme 10).

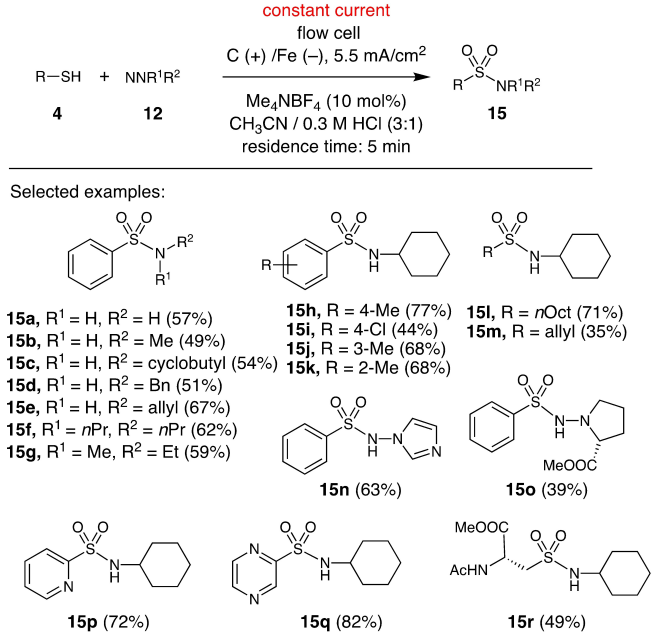
A noteworthy discovery using graphite powder macroelectrodes for the electrochemical synthesis of sulfonamides **15** was made by Menezes and co-workers in 2020.[46] This development showed that the use of inexpensive sodium salts of sulfinic acid can produce sulfinyl radicals through electrochemical oxidation process. The formation of sulfinyl radicals was determined by voltammetry studies. The reaction was carried out under constant current in a compartment cavity cell charged with graphite powder as anode mixed with sodium *p*-toluenesulfinate using an aluminium rod of the cavity diameter placed over the reaction mixture. Then the amine was added dropwise to the compressed mixture. After that, the glass compartment was screwed to a Teflon base to which the solution of the supporting electrolyte was added. Finally, a



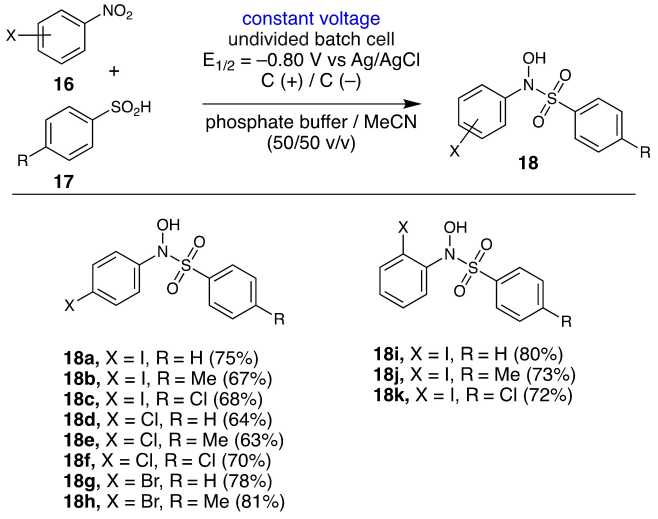
Scheme 7. Potentiostatic batch synthesis of sulfonamides in a divided cell.



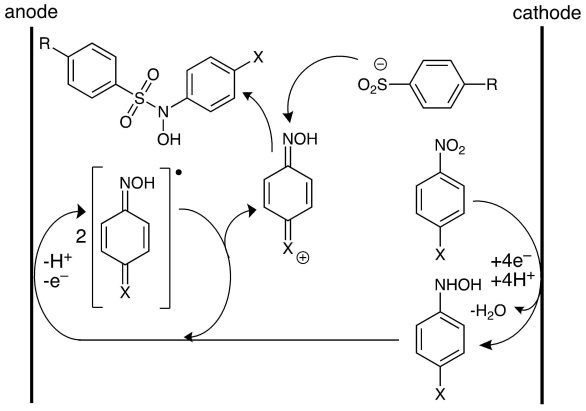
Scheme 8. Galvanostatic batch synthesis of sulfonamides in an undivided cell.



Scheme 9. Flow electrochemical synthesis of sulfonamides.



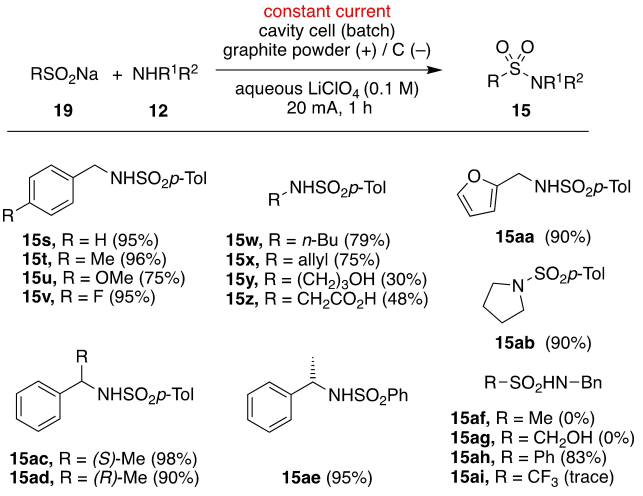
Scheme 10. Electrochemical synthesis of sulfonamides in an undivided batch cell under potentiostatic reaction conditions.



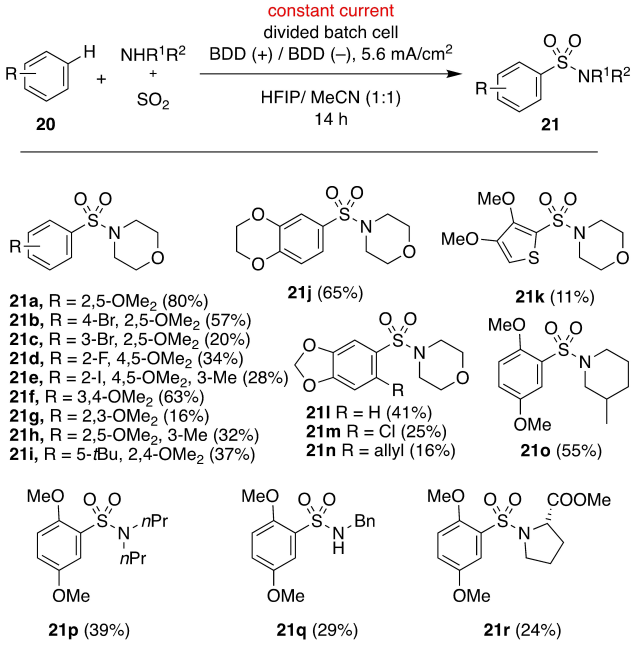
Scheme 11. Proposed mechanism for the electrochemical synthesis of halo-*N*-hydroxysulfonamides.

graphite rod as cathode was immersed. The protocol has been successful in the conversion of a wide range of substrates into their corresponding sulfonamides (Scheme 12).

Very recently, a novel protocol for the electrochemical dehydrogenative sulfonamide synthesis from electron-rich aromatic compounds, amines and SO_2 was reported by Waldvogel and co-workers.[47] In this case, an *in situ* formed amidosulfinate intermediate served the dual role of nucleophile and supporting electrolyte. The replacement of costly SO_2 source such as DABSO[48] by atom economic stock solutions of SO_2 offered an interesting aspect. Optimal results of the SO_2 functionalization were achieved using a divided cell under galvanostatic reaction conditions. As shown in Scheme 13, 36 different examples were reported including a large-scale operation.



Scheme 12. Electrochemical synthesis of sulfonamides in a cavity cell.



Scheme 13. Galvanostatic synthesis of sulfonamides in a divided batch cell.

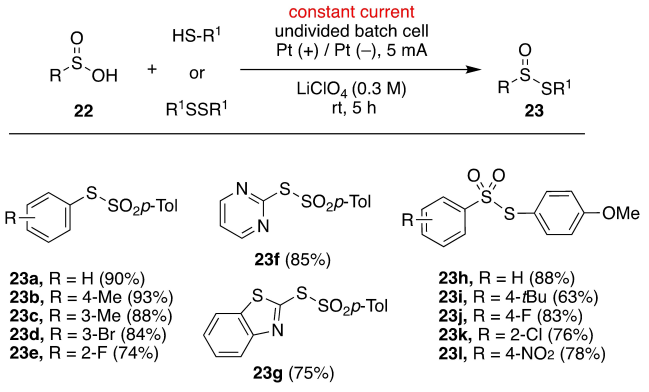
5. Electrochemical Synthesis of Thiosulfonates

In 1840, Weidmann and Lowig reported the first thiosulfonates and then it took almost a century before chemists became interested in these compounds. In 1949, their antimicrobial activities were studied.[49] Thiosulfonates are structural motifs in the antibacterial agent allicin.[50] Thiosulfonates exhibit also biological properties such as antifungal, antimicrobial[51,52] and anticancer activities,[53] and also used as cysteine scanning reagents.[54,55] Recently, thiosulfonates have

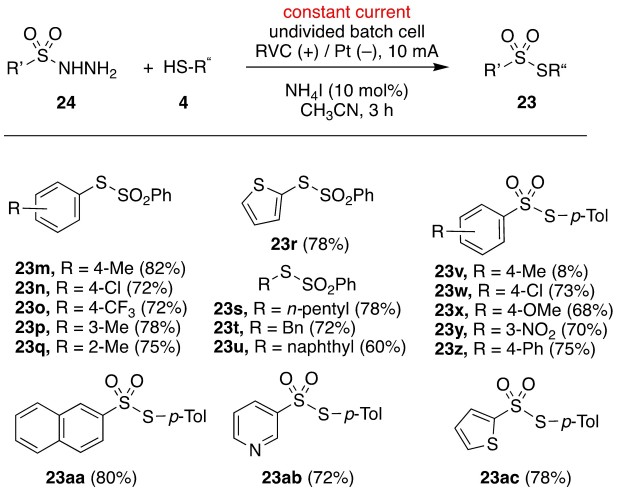
been used as synthetic precursors to incorporate sulfones and thioethers into organic molecules.[56]

An efficient synthesis of thiosulfonates **23** via electrochemical oxidative cross-dehydrogenative coupling of thiophenols or disulfides with arylsulfinic acids **22** was reported by the Sun and co-workers in 2019 through the generation of a superoxide radical anion from water.[57] Many thiosulfonates were synthesised in good yields (Scheme 14). The reaction was conducted with thiophenols or disulfides along with sulfinic acids in acetonitrile using $LiClO_4$ as electrolyte. A similar approach for symmetrical thiosulfonates from thiols or the intermediate disulfides was examined by Wu and co-workers.[58] In both approaches undivided batch cells with platinum electrodes were used. The use of diselenides as precursors under the optimal conditions led to selenosulfonate products. Due to the high diselenide reactivity, the reaction proceeded much faster.

In 2018 Chen and co-workers[59] also published a method for the synthesis of thiosulfonates **23** through the electrochemical sulfonylation of thiols with sulfonyl hydrazides **24** in the presence of iodide as redox catalyst. Mechanistic studies showed that the reaction proceeds through a radical pathway. The oxidation of thiols to thiyl radicals occurred in presence of iodine while the anodic oxidation of sulfonyl hydrazide generated sulfonyl hydrazide radicals, followed by nitrogen elimination to give the sulfonyl radical (Scheme 16). A series of aryl/alkyl/heteroaryl thiols and aryl/heteroarylsulfonyl hydrazides were suitable substrates for this process giving products **23** in excellent yields (Scheme 15).



Scheme 14. Galvanostatic synthesis of thiosulfonates **23** in undivided batch cells.

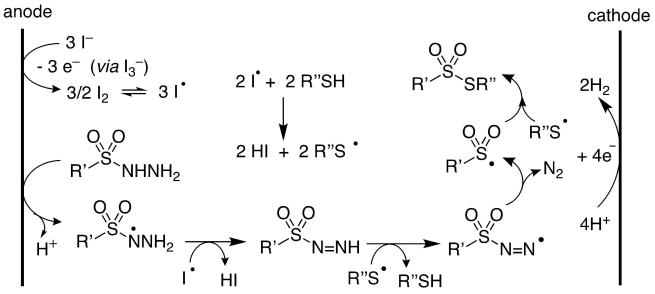


Scheme 15. Electrochemical synthesis of thiosulfonates **23** in an undivided batch cell.

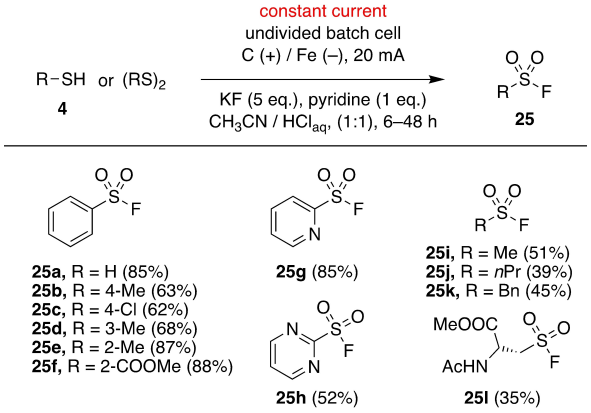
6. Electrochemical Synthesis of Sulfonyl Fluorides

The reactivity of sulfur(VI) fluorides has been recognized a long time ago.[60,61] As attractive precursors for click chemistry they have been of particular interest.[62] Sulfonyl fluorides have also been used as covalent inhibitors in chemical biology[63] and been successfully applied as radiolabeling agents,[64] fluorinating reagents[65] and have been involved in other transformations[66] including polymerizations.[67] This functional group is thermally stable and resistant to reduction compared to other functional moieties such as sulfonyl chlorides.

A novel electrochemical fluorination of sulfonyls via an oxidative coupling of S–F was developed in 2019 by the Noël group.[68] Inexpensive thiols or disulfides were used along with potassium fluoride as a safe and abundant fluoride source. The synthetic protocol uses carbon anodes and stainless-steel cathodes and is providing sulfonyl fluorides **25** without any additional catalyst or oxidant. In an electrochemical flow reactor, complete conversion was observed in just 5 minutes (Scheme 17).



Scheme 16. Suggested mechanism for the electrochemical synthesis of thiosulfonates *via* an iodide mediator.

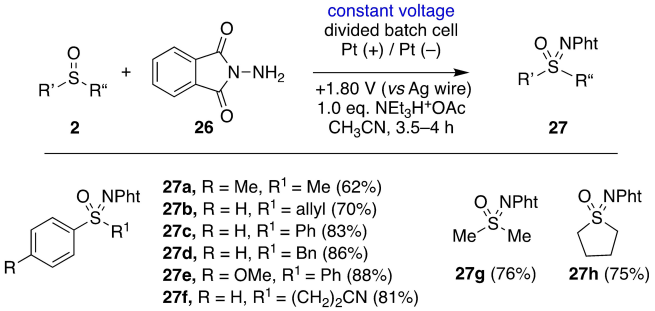


Scheme 17. Electrochemical preparation of sulfonyl fluorides in undivided batch and flow cells.

7. Electrochemical Synthesis of Sulfoximines

In 1949, Bentley and co-workers prepared the first sulfoximine.[69,70] Methionine sulfoximine (MSO) was also identified as the first compound which has high biological effects.[71] Various studies on their application in medical chemistry have been reported recently.[72] Being mono-aza analogues of sulfones, sulfoximines are constitutionally and configurationally stable compounds which can be manipulated without special care[11] but have different reactivity compared to sulfones because of the presence of stereogenic sulfur atom, a nucleophilic nitrogen and acidic α-hydrogen atoms.[71,73]

Yudin and co-workers developed an interesting method for the amination of sulfoxides in batch electrolysis using a divided cell with platinum electrodes in a potentiostatic anodic oxidation.[74] In this case, *N*-aminophthalimide was used as the nitrogen source. The substrates were charged into the anodic compartment and electrolysed with constant current. The products **27** were obtained in good yields (Scheme 18).



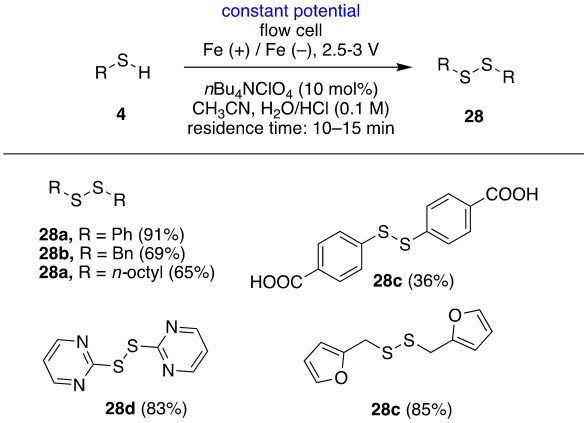
Scheme 18. Electrochemical synthesis of sulfoximines in a divided batch cell under potentiostatic reaction conditions.

8. Electrochemical Synthesis of Disulfides

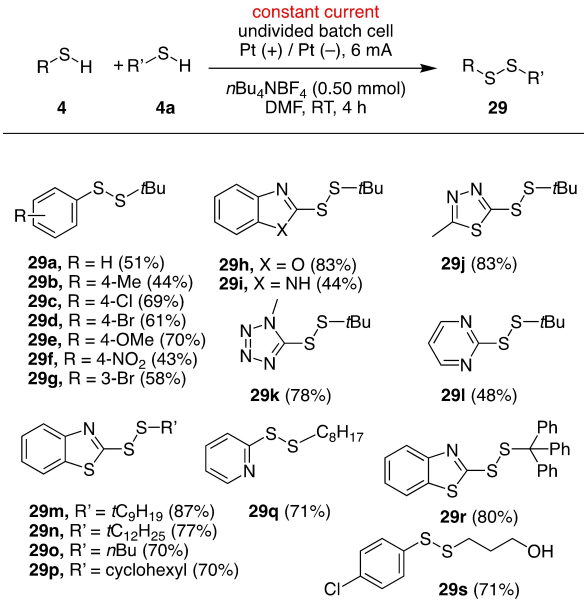
Disulfides are very important moieties in many different types of natural products,[75] organic molecules,[76,77] materials science,[78,79] and pharmaceutical compounds[80] which have shown high activity as antioxidants,[81] antitumour,[82] anti-inflammatory[83] and antiulcer compounds.[84] Also, organo-disulfides are used as catalysts,[85] in ligand exchanges[86] and as protecting groups. The disulfide chemistry also is being used in constitutional dynamic chemistry (CDC)[87] and dynamic combinatorial chemistry (DCC).[88]

In 2017, Noël synthesised symmetric disulfides 28 by using the same protocol for the synthesis of sulfoxides and sulfones (Scheme 1).[21] The reaction is performed in an undivided flow cell under constant voltage and controlled residence time. This protocol was successful to transform 8 examples of thiols into their disulfide in moderate to excellent yields (Scheme 19).

Subsequently, in 2018 Lei and co-workers developed a novel method for S–H/S–H cross-coupling to synthesise unsymmetrical disulfides.[89] The reaction utilized an undivided cell under constant current reaction conditions with platinum electrodes and the addition of a supporting electrolyte. Various heterocyclic mercaptans and thiophenols were screened using an 1:1 ratio of aryl thiol and alkyl thiol substrates. Also, primary, secondary, and tertiary alkyl thiols were successful converted including gram-scale synthesis (Scheme 20). The same electro-oxidative synthesis of unsymmetrical disulfides from thiols was investigated by Xu and co-workers using the same method as shown in Scheme 4 for the synthesis of sulfoxides and sulfones.[23] Also, the same concept was reported by Hilt and co-workers by mixing two, three and six different disulfides using electrolysis.[90]



Scheme 19. Electrochemical synthesis of disulfides in flow electrochemistry using potentiostatic reaction conditions.



Scheme 20. Electrochemical synthesis of disulfides in an undivided batch cell.

9. Conclusions and Outlook

Organosulfur compounds are at the core of several pharmaceuticals, in medicinal applications and chemical transformations that have enabled us to take an interest in them. Efficient electrochemical oxidation protocols for the formation of different organosulfur compounds in past 10 years have been discussed in this review. Different equipment such as batch-type cells and flow cells, electrodes materials and reaction media were successfully optimised in various transformations such as developing one-step protocols for the synthesis of sulfoxides, sulfones, sulfinic esters, sulfonamides, thiosulfonates, sulfonyl fluorides and sulfoximines. The use of electrochemical flow reactors typically leads to much shorter reaction times and the requirement of reduced amounts of supporting electrolytes. Electrochemical organosulfur chemistry is a growing field and will attract more attention in future. The use of flow reactors in the development of versatile electrochemical methods for the broad synthesis of organosulfur compounds synthesis will have to be addressed in future. Additionally, *in situ* electrochemical oxidation of organosulfur compounds for their use in catalysis will be the course of future investigations.

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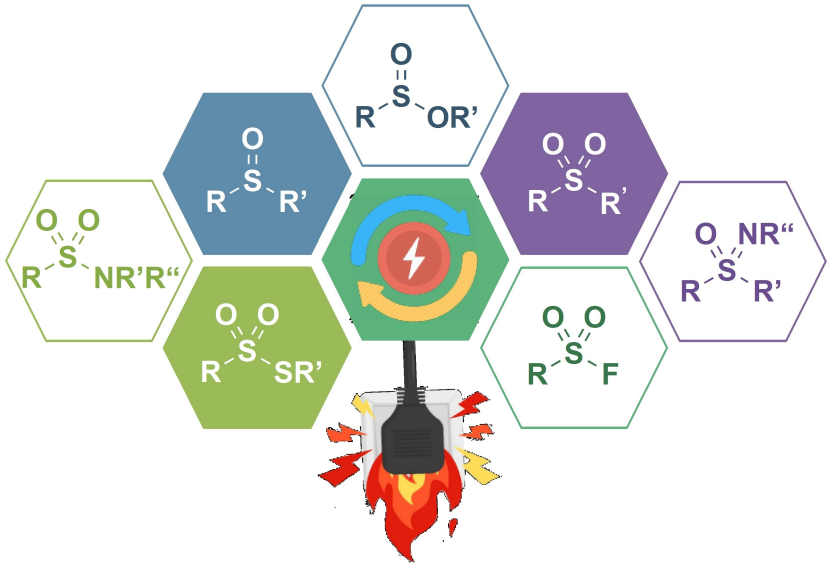
RECORD REVIEW

*N. Amri, Prof. Dr. T. Wirth**

1 – 13

Recent Advances in the Electrochemical Synthesis of Organosulfur Compounds



Electrochemistry offers a green, sustainable and safe alternative to synthesise organosulfur compounds. This review summarises recent developments in the preparation of sulfoxides, sulfones, sulfinic esters, sulfonamides, thiosulfonates, sulfonyl fluorides and sulfoximines under electrochemical reaction conditions.